REMARKS

Applicants acknowledge the withdrawal of the objection to the abstract.

Claims 1 and 6-24 stand rejected under 35 U.S.C. § 103 over Yelton et al in view of Huse et al or Osbourn et al or Winter et al. Claims 1 and 6-24 also stand rejected under 35 U.S.C. § 103 over Lowman et al.

Applicants herewith submit a declaration pursuant to 37 C.F.R. 1.131, along with Exhibit A and Exhibit B, in which the Applicants describe an experiment encompassing all the steps of Claim 1 prior to the effective prior art dates of Osbourn et al and Lowman et al. As such, Applicants submit Osbourn et al and Lowman et al are not prior art to the Applicants' pending claims.

AMENDMENTS TO THE CLAIMS

Claim 1 has been amended to recite the features of Claim 16, which has been cancelled. Further, support for the amendments to Claim 1 can be found in previously cancelled Claim 3 which was part of the original Specification and on page 27 through page 28 lines 1-9. In addition, the feature of Claim 1 reciting "wherein said library comprises about 10^4 or more of different binding molecule species" which was previously added in response to the Rejection mailed 11/16/2004 has been removed. For the reasons stated below, Applicants believe the feature was unnecessarily added and believe Claim 1 as presently pending is neither anticipated nor obvious in view of the cited art.

Claims 6, 9, 13 and 17 have also been amended to properly depend from Claim 1. To further clarify the invention, Claim 18 has been amended to recite "solid support" instead of "solid surface." Support for this amendment can be found throughout the Specification, more specifically on page 44, lines 30-32. Applicants submit no new matter has been added as the claims have been amended to either include the features of previously presented claims or to correct dependencies.

In addition, Claim 25 has been added. Support for Claims 25 can be found throughout the Specification, more specifically on page 18, lines 1-10 and as such, Applicants submit no new matter has been added.

THE INVENTION

The invention is directed to a method in which a solid support coated with an anti-immunoglobulin reagent is used to capture a phage expressed antibody library. The captured phage expressed library is then used to identify one or more bound antigen(s) and/or antibody(ies). The present invention allows one to screen a phage expressed antibody library against multiple ligands simultaneously and identify the different ligands. In addition, the present invention allows the antibodies that bind these ligands to be identified. Further, the present invention provides the benefits of greater sensitivity in binding the expressed antibody library with the use of an anti-immunological reagent and the benefit of the decreased background when screening.

REJECTIONS UNDER 35 U.S.C. § 103

35 U.S.C. § 103 rejection over Yelton et al in view of Huse et al or Yelton et al in view of Osbourn et al or Winter et al

Claims 1 and 6-24 are rejected under 35 U.S.C. § 103 over Yelton et al in view of Huse or in view of Osbourn et al or Winter et al.

Applicants respectfully disagree that a prima facie case of obviousness has been established as Applicants submit the Examiner has not correctly characterized the disclosure of Yelton et al and Huse et al. The cited references, alone or in combination, do not disclose all the features of Claim 1 and as such, the cited references do not anticipate nor render obvious the pending claims. Specifically, the cited references alone or in combination do not disclose or suggest providing a solid support coated with an *anti-immunoglobulin reagent*. In addition, the cited references do not suggest or provide motivation to combine the cited references to arrive at the present invention.

In addition, Applicants herewith submit a declaration pursuant to 37 C.F.R. 1.131 describing an experiment encompassing all the steps of Claim 1 prior to the prior art effective

dates of both Lowman et al and Osbourn et al. Applicants submit these references cannot properly be used as prior art to the present application.

The Examiner has incorrectly characterized the disclosure of Yelton et al and Huse et al.

In the Rejection mailed 11/16/2004 (page 4) and reiterated in the Rejection mailed 8/10/2005 (page 4), the Examiner states:

> Yelton et al discloses at page 19, line 11 up to page 20, line 7, a method of contacting nitrocellulose filters (solid support, as claim) blocked with a blocking buffer (page 26, lines 22-26) to prevent nonspecific binding of antibodies and coated with goat anti-human kappa light chain conjugated to alkaline phosphatase. And then conjugated with phage BR antibody library. See further the cited Huse reference which describes the coating of support. (Rejection mailed 8/10/2005, page 4)

Applicants submit Yelton et al does not disclose a solid support coated with goat anti-human kappa light chains conjugated to alkaline phosphatase which then is contacted with a phage BR antibody library as alleged by the Examiner. Specifically Yelton et al discloses

> Fab expression was induced by overlaying each plate with a 0.45 μ nitrocellulose filter (Schleicher & Schleicher, Keene, NH) that had been soaked in 10 mM isopropyl-β-D-thiogalactopyranoside (IPTG) (Boehringer Mannheim). Plates were incubated at room temperature from 6 hr to overnight. *The filters were then removed and processed by immunoblotting techniques*. . . First, the filters were blocked in blocking buffer (Biosite, San Diego, CA) to prevent nonspecific binding of antibodies. The filters were then incubated 1-2 hr at room temperature with goat anti-human kappa light chain conjugated to alkaline phosphatase. . . . (Yelton et al, page 19, line 56-page 20, lines 1-7) (emphasis added)

The filter in Yelton et al is first coated with Fabs, then subjected to immunoblotting techniques. It is not until after the filter is coated with the Fabs and then blocked with blocking buffer that the goat anti-human kappa light chains conjugated to alkaline phosphatase is added. Similarly, Huse et al also discloses expressing Fabs directly onto a membrane, which is then blocked and to which goat anti-human immunoglobulins are added. (Huse et al, page 3915). As such, Applicants respectfully submit that Yelton et al and Huse et al do not provide the factual support alleged by the Examiner and cannot therefore, provide a proper basis for a prima facie case of obviousness.

The cited references do not teach or suggest all of the features of the pending claims.

In addition, the disclosures provided by the cited references do not render the pending claims obvious as the references do not teach or suggest all of the limitations of the pending claims. The references, alone or in combination, do not teach providing a solid support coated with an anti-immunoglobulin reagent prior to contacting with a phage expressed library. As demonstrated above, Yelton et al and/or Huse et al do not coat a membrane with anti-immunoglobulin reagents prior to contacting the solid support with a phage expressed library. Yelton et al discloses membranes coated with L6 Fabs, L6 with BR96 light chains, or BR96 libraries (for example see page 19, lines 55-58 to page 20, lines 1-7, Page 21, lines 34-42 and page 25, lines 22-26, respectively). The L6 Fabs are directed against a tumor-associated cell surface antigen expressed by many human carcinomas (Huse et al, page 3914). The BR96 and the BR96 mutant antibodies are directed to the Lewis Y moiety of a tumor antigen expressed on many carcinomas and carcinoma derived cell lines. (Yelton et al, page 24, lines 14-15). The L6 Fabs, L6 with BR96 light chains, BR96 or BR96 mutant antibodies are therefore not anti-immunoglobulin reagents as they are directed to tumor antigens. Yelton et al therefore does not provide disclosure of providing a solid support comprising a membrane coated with an *anti-immunoglobulin reagent* as recited in Claim 1.

Similarly, Huse et al, which is referenced by Yelton et al, does not disclose providing a solid support comprising a membrane coated with an anti-immunoglobulin reagent as Huse et al discloses expressing Fabs directly onto a membrane, which is then blocked and to which goat anti-human immunoglobulins are added. (Huse et al, page 3915). Huse et al therefore does not cure the deficiency of Yelton et al.

Winter et al also does not teach a solid support coated with an anti-immunoglobulin reagent before a phage expressed antibody library is contacted with the solid support as recited by the Applicants claims. As stated in the page 4-5 of the Office Action mailed 8/10/2005, Winter et al allegedly discloses a library of about 10^5 different VH. Applicants submit Winter et al does not cure the deficiencies discussed above of Yelton et al or Huse et al as it does not disclose providing a solid support comprising a membrane, with the membrane coated with an anti-immunoglobulin reagent.

The cited references do not provide motivation to combine the references to arrive at the claims invention.

Further, the cited references also do not provide motivation to arrive at the Applicants' invention. Yelton et al and Huse et al use goat anti-human antibodies for detection of antibodies from a library expressed directly onto a nitrocellulose membrane. The purpose of the anti-immunoglobulin reagent bound on a membrane in the present invention is to capture a phage expressed library. As Applicants demonstrate in Example 2 of the Specification (pages 45-46, results in Figure 2), the use of an anti-immunoglobulin reagent increases the amount and number of captured antibodies from the phage expressed library when compared to expression directly onto a membrane in the absence of an anti-immunoglobulin reagent. As mentioned above, Yelton et al and Huse et al use a goat anti-human antibody for detection, an entirely different purpose than that of Applicants' invention. As such, the disclosures of Yelton et al and Huse et al would not suggest or provide motivation to use an anti-immunoglobulin reagent as a method of capturing an antibody instead of as a detection reagent.

Applicants submit that the cited references, individually and in combination, do not disclose or suggest all the features of Applicants' Claim 1. In addition, the cited references do not suggest nor provide motivation to combine the cited references to arrive at the present invention. As such, Applicants respectfully submits that the Examiner has not established a prima facie case of obviousness and Applicants respectfully request the withdrawal of the present rejection.

35 U.S.C. § 103 Rejection over Lowman et al

Claims 1 and 6-24 stand rejected under 35 U.S.C. § 103 over Lowman et al.

A reference against a generic claim may be antedated by a declaration under 37 C.F.R. 1.131 showing completion of the invention of only a single species within the genus, prior to the effective date of the reference. Ex parte Biesecker, 144 USPQ 129 (Bd. App. 1964)

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Applicants herewith submit a declaration pursuant to 37 C.F.R. 1.131, along with Exhibit A and Exhibit B, which establishes a reduction to practice of an experiment encompassing all the steps of the claimed method prior to July 2nd, 1997, the effective prior art date of Lowman et al. In addition, as Applicants have established a reduction to practice prior to July 2nd, 1997, Applicants have also antedated Osbourn et al, which Applicants submit has an effective date of July 8th, 1997.

Applicants submit Exhibit A (Experiment #100) describes an experiment in which a phage expressed library derived from human lymph node tissue captured on a nitrocellulose membrane was used to screen a sample made from cell expressing tumor antigens. Applicants have provided Exhibit B (Experiment #92) as steps 1-3 of Exhibit B specifically describe how a nitrocellulose membrane was coated with goat anti-human kappa antibodies. Applicants therefore submit the herewith submitted declaration pursuant to 37 C.F.R. 1.131 and the accompanying exhibits antedate Lowman et al and Osbourn et al and as such, Lowman et al and Osbourn et al cannot properly be used as prior art to the present claims.

Specifically, step 1 of Exhibit A discloses the feature of Claim 1 of providing "**a solid support coated with an anti-immunoglobulin reagent, wherein said solid support comprises a membrane**" as the "capture lift" described is a nitrocellulose membrane (solid support which is a membrane) coated with goat anti-human kappa antibodies (anti-immunoglobulin reagent). Exhibit B, submitted herewith, describes the procedure used to prepare the "capture lift" as referenced in step 1 of Exhibit A. As indicated in steps 1- 3 of Exhibit B, a nitrocellulose filter is first coated with goat anti-human kappa antibodies. Therefore, the "capture lift" of step 1 of Exhibit A is a solid support coated with an anti-immunoglobulin reagent wherein the solid support is a membrane.

In addition, step 2 of Exhibit A discloses the feature of Claim 1 of providing "**a phage expressed antibody library**" as the "lymph node library" referenced in the title of the experiment is a phage expressed library of human IgG1/κ Fabs derived from human lymph node tissue. The 240H2 referenced is a clone expressing a Fab that serves as a positive control as the Fab is specific for the Le^Y tumor antigen found on many tumor cells.

Further, step 5 of Exhibit A describes the feature of Claim 1 of **"contacting said solid support and said phage expressed antibody library to generate an antibody bound solid support"** as the "capture lift" (the solid support coated with an anti-immunoglobulin reagent) is overlaid (contacted) onto a plate on which a sample of the phage expressed antibody library has been spread (S50 plate). The placing of the "capture lift" (nitrocellulose membrane coated with goat anti-human kappa antibodies) on the plate spread with dilutions of phage expressed Fabs from a "lymph node library" (phage expressed antibody library) results in a nitrocellulose membrane coated with goat anti-human kappa antibodies with captured human Fabs (antibody bound solid support).

Step 6 and step 7 of Exhibit A describes the feature of Claim 1 of **"contacting said antibody bound solid support with a sample containing one or more antigens, wherein said contacting generates a solid support containing antibody-antigen complexes."** Specifically, step 6 describes a biotinylated membrane sample made from cells expressing tumor antigens which is incubated with the "capture lift" containing bound Fabs from the phage expressed "lymph node library" from step 5 of Exhibit A (antibody bound solid support). The incubation of the "capture lift" with the membrane preparation of step 6, which contains one or more tumor antigens (sample containing one or more antigens), results in the binding of antigens to the Fabs bound to the nitrocellulose membrane through the goat anti-human kappa antibodies (contacting generates a solid support containing antibody-antigen complexes).

Step 7 of Exhibit A describes the feature of Claim 1 of **"identifying one or more antibody-antigen complexes"**. Specifically, step 7 describes adding a dilution of strepavidin alkaline phosphatase which will bind to biotinylated proteins (from the membrane preparation of step 6) which have been bound to Fabs from the phage expressed library (antibody-antigen complexes). The strepavidin-alkaline phosphatase conjugate allows one to visualize those Fabs from the phage expressed library that have bound antigens, thereby allowing the identification of one or more antibody-antigen complexes as recited in Claim 1.

Applicants submit the declaration submitted herewith discloses an experiment encompassing all of the steps of pending Claim 1, which was reduced to practice prior to the effective prior art date of Lowman et al. As such, Applicants submit that Lowman et al is not prior art. As Lowman et al is not prior art, Applicants submit the rejection is moot and respectfully request the Examiner withdraw the rejection.

Amendment to Claim 1- removal of the previously added feature of "wherein said library comprises about 10^4 or more of different binding molecule species"

Applicants have removed the feature of Claim 1 reciting "wherein said library comprises about 10^4 or more of different binding molecule species, " added in response to the Rejection mailed 11/16/2004. Upon further review of the cited art, Applicants believe the amendment was unnecessary for the following reason. Specifically, as described above, neither Yelton et al nor Huse et al (mentioned in Yelton et al) provides disclosure of providing a solid support comprising a membrane which is coated with an **anti-immunoglobulin reagent**, thereby failing to disclose all of the features of the Applicants' pending claims required to anticipate. As discussed above, Yelton et al and Huse et al describe expressing a library directly onto a nitrocellulose membrane and then detecting the bound antibodies with a goat anti-human antibody. Yelton et al and Huse et al use the goat anti-human antibody for detection and not for capture of a phage antibody library as in the Applicants' claims. As such, Applicants believe that neither Yelton et al nor Huse et al anticipate the pending claims.

CONCLUSION

Applicants submit the present claims are not obvious over Yelton et al in view of Huse or Winter et al nor are they anticipated by Yelton et al or Huse et al as the references, alone or in combination, do not disclose or suggest all of the features of Applicants' claims. Further, Applicants have antedated Lowman et al and Osbourn et al and as such, Lowman et al and Osbourn et al are not prior art to Applicants' claims. Applicants respectfully request that the rejections be withdrawn and the claims allowed. Should the Examiner wish to discuss the foregoing in an effort to advance this application towards allowance, the Examiner is urged to telephone the undersigned at the indicated number.

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